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13. ABSTRACT (Maximum 200 Words) ATLAS - an international trial designed to assess the optimal duration of adjuvant tamoxifen - received its original funding by the US Army in 1995. Following the approval of the final report, a further year's funding was awarded. The current report covers the work done with the additional funding. ATLAS remains on course to achieve its overall objectives. More than 400 hospitals have ethics approval, and more than 300 centres are randomising women into the trial. With the implementation of the ATLAS Patient Identification and Registration Project, ATLAS has systematically identified more than 7000 women who are currently on tamoxifen and who are eligible for entry either now or at some time in the future to ATLAS - the registration target is 30,000, which will be reached during the next 2-3 years. At 06/2000, more than 6000 women have been randomised - ATLAS should reach its accrual target in 2005. Follow-up will continue at least until 2010, when the main results of the trial will be reported. The ATLAS Oestrogen Receptor Detection Project is now being implemented to ensure that the ER status of all randomised women in ATLAS is ascertained. The independent Data Monitoring Committee for ATLAS convened in June 1999, when it endorsed the continuing importance of ATLAS and confirmed that the trial was progressing satisfactorily. For ATLAS to achieve its main objectives, additional funding is required and is requested as part of this report.				
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FOREWORD

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Richard Peto

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A. INTRODUCTION: ATLAS 1995-2010

ATLAS: 1995-2000 done; 2000-2005 randomisations still to be funded

ATLAS (Adjuvant Tamoxifen - Longer Against Shorter), a large international randomised trial of tamoxifen duration in early breast cancer that began in 1995, will continue randomising until 2005 and will report its main results in 2010, received its initial four years of funding through the US Army Breast Cancer Research Program (Grant number DAMD 17-94-J-4422). The final report on the first grant was approved, and one year's additional funding was awarded to allow the study to continue.

The current report summarises the work undertaken during the one-year extended funding period from 1999-2000. The trial is well on its way to meet its main objectives, but continued funding is still required and is being requested as part of this report.

Summary of progress

The worldwide randomised evidence now shows that a few years of adjuvant tamoxifen, following the initial management of early breast cancer, reduces the risk of relapse and improves long-term survival. A recent publication in the Lancet has reported dramatic reductions – more than 25% in the last decade – in breast cancer mortality in the UK and US, which can be attributed in large part to the wider use of tamoxifen¹. Moreover, at least 5 years of tamoxifen reduces the risk of relapse and may also improve long-term survival² to a greater extent compared with shorter regimens. However, there is substantial uncertainty as to whether more than 5 years of hormonal treatment produces additional benefit³.

ATLAS is designed to assess reliably the balance of benefits and risks of prolonging adjuvant tamoxifen by an extra 5 years in women for whom, after about five years of treatment, there is uncertainty as to whether they should stop their tamoxifen now, or continue for several years longer. About 20 000 eligible women who have usually had about 5 years of adjuvant tamoxifen are to be randomised in ATLAS either to stopping their tamoxifen, or continuing it for 5 more years and then followed for at least 10 years to allow sufficient time for the overall balance of benefits and hazards of longer or shorter adjuvant tamoxifen treatment to emerge.

With the US Army funding, major progress has been made towards fulfilling the primary objective of the ATLAS trial. Under the direction of the coordinating centre (i.e. Oxford Clinical Trial Service Unit), an international network of clinicians has been established:

Centres with ethics IRB approval: more than **400** centres in more than 30 countries worldwide now have ethics/IRB approval. At the time of the final report, there were just 335 centres – some of the additional centres result from the recent extension of ATLAS into the United States.

Centres randomising women into ATLAS: There are now **319** sites actively entering women into the study (compared with 246 at the time of the previous report).

Numbers of women randomised: More than **6200** women have been randomised by June 2000 (compared with 3500 towards the end of 1998 when the previous report was submitted), and accrual

rates are increasing rapidly. Furthermore, ATLAS is now being extended to countries where accrual is likely to be substantial, in particular, China. If continued support is made available, then the accrual target of about 20,000 will be reached by 2005, and all randomised women are to be followed up with the main results being reported in 2010.

Of crucial importance since the previous the **ATLAS Patient Identification and Registration Project** and the **ATLAS Oestrogen Receptor (ER) Detection Project** have been planned and implemented: the aim of the former is to identify systematically potentially eligible women who are currently on tamoxifen and who could either be randomised now or at some future point into ATLAS. **Already more than 7000 women have been registered**, and large-scale registration will continue during 2000-3. The aim of the ER Detection Project is ensure that the oestrogen receptor status is available on as many women randomised in ATLAS as possible to avoid the risk of a false negative result in ATLAS. (Further details of the rationale to this project are set out in the report.)

The future: At the meeting of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in September 2000, a consensus should be maintained that 5 years of adjuvant hormonal treatment is definitely better than just 2 years. The need for better evidence on the important question of whether 10 years is better than 5 year is, however, likely to be reconfirmed, which is likely to stimulate further interest in ATLAS (and thus increase accrual). ATLAS national collaborators' meetings worldwide from September 2000 onwards are now being organised at which the new EBCTCG results will be presented and ATLAS re-launched. Following the randomisation of about 20,000 women (by the year 2005), they will need to be followed up for many years (at least until 2010) until a clear answer emerges. Procedures are now in place for ensuring reliable long-term follow-up of women randomised, and the annual follow-up cycles conducted so far have demonstrated their feasibility in terms both of acceptability (from a workload perspective) to clinicians and of completeness of data. Compliance with allocated study treatment is good in both arms of the study.

ATLAS is the largest ever trial of tamoxifen duration and the study is now well on its way to establishing whether prolonging tamoxifen beyond the first 5 years provides additional benefit - a question that has not been addressed adequately in the other small trials of 5 versus 10 years of tamoxifen. If ATLAS demonstrates that longer treatment confers extra benefit, then this has the potential to avoid several thousand extra breast cancer deaths each year. And, on the contrary, if ATLAS shows that 5 years is sufficient, then this could avoid the unnecessary treatment of hundreds of thousands of women worldwide.

With US Army funding, international collaboration on a massive scale is now a reality. In common with all cancer treatment trials with survival as the primary outcome, this is a long-term project. To maintain the collaboration and to achieve the accrual target and long-term follow-up, additional funding is still needed. In the previous report, 3 years of extra financial support were requested but even though the external scientific reviewer endorsed this need, only one year's additional funding was awarded. Such funding was welcome and important in helping ATLAS to extend and strengthen the collaboration and to start additional projects that enhanced the original aims (for example, the Registration Project and ER Project). But a study that compares 5 versus 10 years of treatment obviously has to continue for more than 10 years, and continued funding is again requested.

It is implicit that if, the US Army Breast Cancer Research Program is to reap the full benefits of its original investment, it should provide additional funding to help ATLAS continue towards its final aims. Funding has been obtained from other sources (that will be used for activities additional but complementary to these activities), but continued funding from the US Army Breast Cancer Research Program would help to maintain the existing collaboration, but also in particular, to support the process of registration of women and their follow up once randomised in the trial.

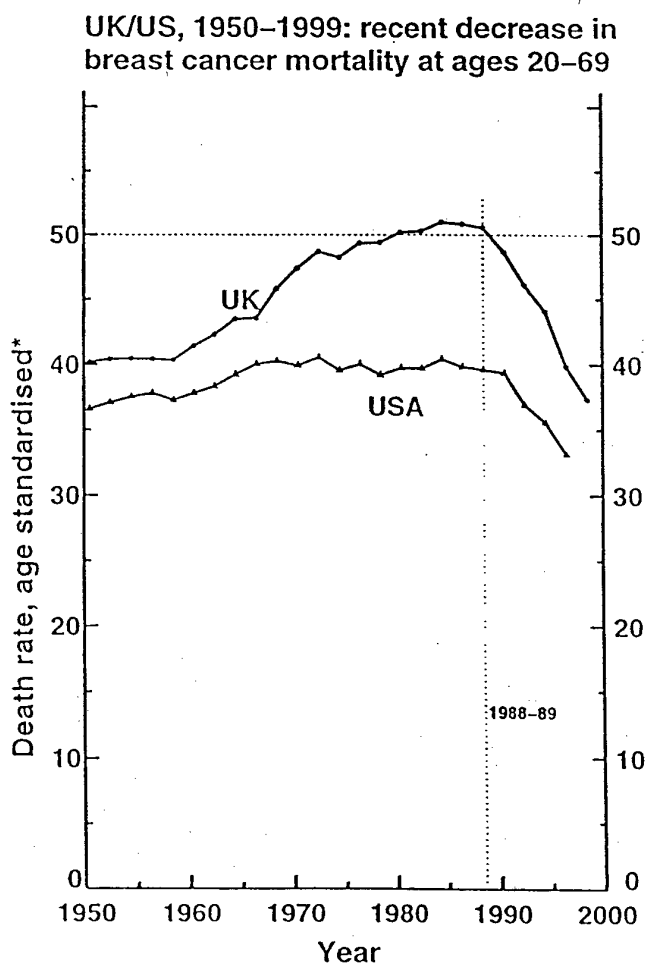
B. DETAILED SCIENTIFIC RATIONALE FOR ATLAS and NEW SUBPROJECTS INTRODUCED SINCE THE FINAL REPORT

The currently randomised evidence on adjuvant tamoxifen

Breast cancer is common with more than 800 000 new cases diagnosed annually worldwide. It is the leading cause of female neoplastic death in most developed countries; and, in developing societies, breast cancer is only second to cervical cancer in cancer deaths. The reliable demonstration that a practicable and widely available treatment for such a common disease produces a moderate improvement in long-term survival (e.g. improving survival by a few per cent from, say, 50% to 52 or 53%) could lead to the treatment of some hundreds of thousands of women, and the consequent delay of several thousand deaths worldwide, each year.

Before the EBCTCG results emerged, there had been little evidence of any decrease in breast cancer death rates over the previous half-century. However, following the demonstration by the EBCTCG meta-analysis in the mid-1980s that tamoxifen confers definite survival benefits⁴, there has been a substantial increase in the use of tamoxifen and now it is estimated that more than one million women worldwide are currently prescribed tamoxifen. This makes it one of the most widely used and effective forms of medical oncology, preventing tens of thousands of breast cancer deaths each year worldwide. At least in those countries where tamoxifen is being widely used amongst women who stand to benefit, decreases in breast cancer deaths are now being experienced: about 30% of deaths from breast cancer have been avoided in the US and UK during the last decade¹. This sudden decrease in breast cancer mortality can be attributed largely to the benefits of improved treatment, particularly with tamoxifen^{1,5,6} (Figure 1).

Figure 1: Breast cancer mortality in the UK and US, 1950-99¹

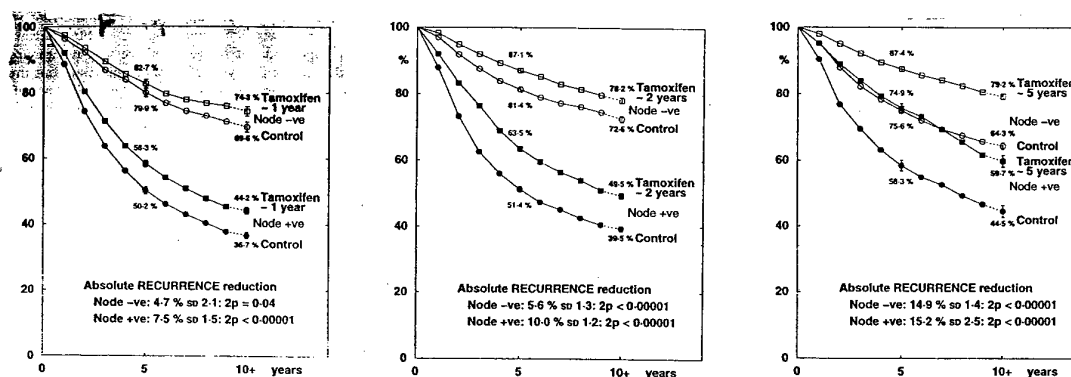


The most recent EBCTCG meta-analysis of 55 randomised trials of adjuvant tamoxifen allowed much more detailed conclusions to be drawn regarding effectiveness². It demonstrated, for women with oestrogen receptor (ER) positive disease and for those with no ER assay available, a highly significant improvement in 10-year survival corresponding to an average of about 5 or 6 fewer deaths per 100 women treated with about 5 years of tamoxifen regardless of age or nodal status – if women who had not received tamoxifen in these trials had not had rescue treatment with the drug on relapse, then this reduction in mortality would have probably been about twice as great. A number of questions remain unanswered, however, regarding the optimal use of tamoxifen. In relation to tamoxifen duration, if this uncertainty is to be resolved, further large-scale further randomised evidence is needed in trials comparing - within the same study - longer versus shorter tamoxifen regimens^{2,3,7}.

The relevance of tamoxifen duration

5 years vs. 1 or 2 years: For recurrence prevention, longer is better: The EBCTCG has so far reviewed only trials of tamoxifen versus no tamoxifen and then amongst these trials, has investigated the relevance of duration². Most trials of tamoxifen have involved 1, 2 or 5 years of tamoxifen vs. no tamoxifen. Within this range, longer tamoxifen regimens seem more effective at preventing or delaying recurrent disease and may also improve long-term survival compared with shorter regimens (Figure 2).

Figure 2: Proportional risk reductions in recurrence during the first 10 years amongst women with potentially hormone-sensitive disease, subdivided by tamoxifen duration²



A second generation of trials comparing 2 years versus generally about 5 years of tamoxifen has been started. These trials should eventually provide reliable evidence on the relative effects of a few extra years of treatment. Preliminary results from such comparisons support the indirect evidence from the EBCTCG overview that, at least for recurrence, longer treatment is more effective^{8,9}. A recently reported trial conducted in France comparing 2 years of tamoxifen with about 7 years produced the same finding, with women who had received longer treatment having significantly reduced rates of recurrent disease¹⁰. However, it will take many years for these relatively small trials to provide a reliable answer in particular with respect to overall survival. The EBCTCG will be reviewing these trials of 2 years of tamoxifen versus longer in September 2000 and, if this shows that 5 years of adjuvant hormonal treatment is definitely better than just 2 years, the question of whether 10 years is better than 5 years will become even more pertinent, and will eventually have to be answered.

5 years versus longer: Still unanswered for recurrence and survival: So far, the net effect of tamoxifen when used for longer than 5 years has not been properly studied either through indirect comparisons of duration between trials of tamoxifen versus no tamoxifen, or through direct comparisons in trials which compare within the same study, 5 years of tamoxifen versus longer treatment³. Concerns have been expressed about tamoxifen resistance¹¹ with more prolonged treatment, but the mechanisms

of resistance are poorly understood and more importantly, so far, this has not been supported by randomised evidence. The current trials are of insufficient size - even in combination (they have recruited just 1700 patients) - to detect the type of moderately sized difference that might exist^{3,7,11-13}. The three directly randomised comparisons that started long enough ago to have produced some results (ECOG, Scottish Cancer Trial and NSABP B-14), have now closed. All three involved only small numbers of breast cancer recurrences or deaths after year 5. (For example, in the most recently available data - up to 1 January 1999 - from the NSABP B-14 trial of 5 versus 10 years of tamoxifen, the total numbers of local, contralateral or distant recurrences after year 5 were only 45 versus 51, respectively, which does not preclude longer treatment being better). It remains quite possible, based on the current evidence available to hope for additional benefit from longer treatment.

But, if this is going to be reliably demonstrated, tens of thousands of women may need to be randomised and followed up for at least 10 years. It will probably not be until 2005 or more likely 2010, that there will be sufficient randomised evidence on 5 vs. 10 years of tamoxifen for review by the EBCTCG. The major deficiency in research evidence and hence, the main uncertainty in clinical practice, lies in the assessment of the effects of prolonging adjuvant tamoxifen beyond 5 years. The fundamental rationale for the ATLAS trial at the time of the original funding application was to address this uncertainty, and it remains appropriate now: for, ATLAS may be the only trial which is large enough to address this question reliably.

Important long-term side-effects of tamoxifen and the relevance of duration

Tamoxifen reduces the incidence of contralateral breast cancer (i.e. secondary prevention) and this effect appears to be more marked with longer treatment². Although no other long-term beneficial side-effects have yet been reliably demonstrated, long-term use of tamoxifen may also have a beneficial effect on coronary heart disease by lowering cholesterol¹⁴⁻¹⁷ and on osteoporosis through its oestrogen effects¹⁸⁻²⁰. While the benefits of tamoxifen are greater with more prolonged therapy, the reliably established adverse long-term side effects may also be affected by the length of treatment. Specifically, the risk of tamoxifen-induced endometrial cancer appears to be increased with more prolonged therapy² and there is a small increased risk of death from thrombo-embolic disease with one extra death from pulmonary embolus per 1000 women treated with about 5 years of tamoxifen². No other major life-threatening or life-prolonging side effects have, as yet, been reliably demonstrated.

Although an increase in endometrial cancer and thrombo-embolic events attributable to tamoxifen seems definite, this is smaller than the definite decrease in contralateral breast cancer. Moreover, the increase in the number of such deaths is much smaller than the absolute decrease in all-cause mortality. For every 1000 women treated with ~5 years of tamoxifen, about 80 breast cancer deaths will be avoided, compared with 2 extra deaths from endometrial cancer and 1 extra death from pulmonary embolus i.e. in terms of overall mortality, tamoxifen is doing about 30 times more good than harm². Hence, the available randomised evidence when considered in its entirety supports the continued use of tamoxifen in the adjuvant setting²¹.

However, both adverse and beneficial effects may increase if tamoxifen is taken for many years, and any assessment of the effects of tamoxifen must address the overall balance of risks and benefits.

Why does ATLAS need to be so large and to have prolonged follow-up?

The reliable demonstration, or refutation, of any plausibly moderate-sized additional advantage that might be produced from longer treatment requires large-scale randomised comparisons. Small-scale randomised evidence carries the substantial risk of undue weight being given to favourable or unfavourable random fluctuations based on few events — particularly if interim analyses are carried out repeatedly and any extreme "zigs" or "zags" produced by chance unduly emphasized²². Long follow-up among a large number of randomised patients is required before sufficient numbers of recurrences and deaths will have occurred to allow reliable comparisons.

But, there is another reason why comparisons of different tamoxifen durations require long follow-up. It is evident from the EBCTCG overview that there is a substantial "carry-over" benefit from tamoxifen lasting beyond the treatment period². A few years of adjuvant tamoxifen produces a reduction in the annual recurrence rate and in the annual death rate not only **during** treatment, but also for a few years **after** treatment has stopped. This persistent benefit **enhanced** the absolute difference in 10-year survival observed in trials of tamoxifen vs. no tamoxifen. However, in trials comparing stopping after a few years versus continuing for longer, this carry-over benefit amongst patients stopping their tamoxifen may mean that, for the first few years of additional treatment, there is little apparent additional benefit from continuing tamoxifen — **even if, later on, a worthwhile benefit from longer treatment emerges**. Consequently, it is imperative that follow-up in such trials is sufficiently long to allow any late survival benefit from continuing tamoxifen to emerge.

Table 1: Example of the numbers of deaths that might be observed in various periods after randomisation of 20 000 women between 5 versus 10 years of tamoxifen

Years since randomization	SHORTER (e.g. stop after ~ 5 years of tamoxifen): 10 000 women	LONGER (e.g. continue for 5 extra years after 5 years of tamoxifen): 10 000 women	Statistical significance of such a result NS = not significant
0-3 years	~1000	~1000	NS
0-6 years	~2000	~1900	NS
0-10 years	~3000	~2750	P<0.0001

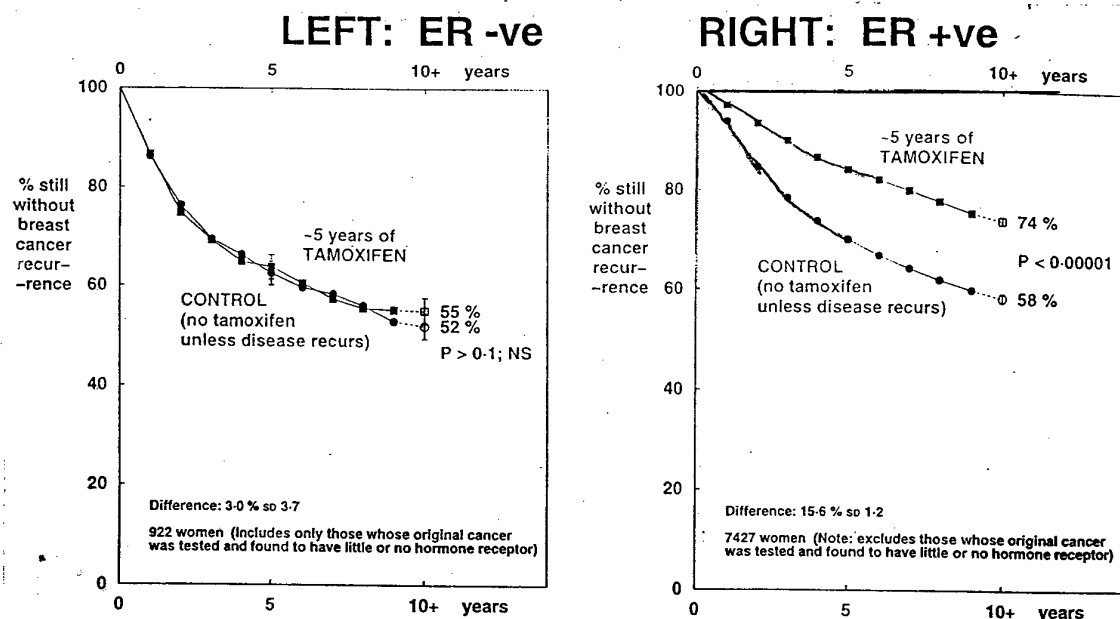
The effect size might be larger than this: if it is, then it may be clearer earlier on.

Rationale for the ATLAS Oestrogen Receptor Detection Project: The importance of establishing the ER status of women randomised in ATLAS

An increasing proportion of the women randomised in ATLAS have already had about 5 years of tamoxifen as adjuvant treatment for their breast cancer prior to randomisation to stop (yielding a total of 5 years of treatment), or to continue for 5 more years (yielding a total of 10 years). ATLAS will randomise at least 10,000 such women between 5 years and 10 years of adjuvant tamoxifen. The key outcome is long-term survival and, although it would be unrealistic to expect a large survival difference (see above), even a 15% reduction in breast cancer mortality (which would translate into a 10% reduction in all-cause mortality, e.g. reducing 25% dead to 22½% dead) might be considered worthwhile by many women and their doctors. If such a difference does exist, we do not want a false negative result.

The 1995 EBCTCG review of the trials of 5 years of adjuvant tamoxifen versus no tamoxifen suggested that, even for recurrence, tamoxifen is of little benefit for women whose original breast cancer was oestrogen receptor (ER) negative (see Figure 3)².

Figure 3: 5 years of tamoxifen versus no tamoxifen, according to oestrogen receptor status



Therefore, trials like ATLAS may well show that 10 years of tamoxifen produces better survival than just 5 years of adjuvant tamoxifen only in women whose original tumour was ER positive. This underlines the importance of knowing the ER status of as many as possible of the women randomised in ATLAS. For, if the effects among women who are ER+ are not separated from those among women who are ER-, then the size of effect in the ER+ women is likely to appear smaller than is actually the case, with the worst case scenario being a false negative overall result that could have been avoided by knowledge of the ER status. This could adversely affect the treatment of several hundreds of thousands of women. If tamoxifen does not confer overall benefit to women whose original breast cancer was ER-, then the treatment effect in the ER- patients in ATLAS will differ only randomly from zero, so it could well be 1 or 2 standard deviations adverse, simply by the play of chance. If this were to happen, it could easily change a clearly significant ($2p < 0.01$) survival difference among the other women into a non-significant result among all women: see Table 2.

Table 2: Hypothetical results for 10,000 randomised women, comparing 5 years versus 10 years of adjuvant tamoxifen, if the results in ER- women are, by chance, 1.5 standard deviations adverse. (The first two columns give deaths after randomisation / numbers randomised at year 5, and the last column gives the difference in the number of deaths, together with its standard deviation and p-value.)

	Allocated 10 years tamoxifen	Allocated 5 years tamoxifen	Mortality difference (& 2p value)
ER+ (or ER untested)	900/4000 (22.5%)	1000/4000 (25%)	100 SD 38 ($2p < 0.01$)
ER- (by the proposed additional ER assays)	280/1000 (28%)	250/1000 (25%)	-30 SD 20 ($2p > 0.1$)
All women	1180/5000 (23.6%)	1250/5000 (25%)	70 SD 43 ($2p > 0.1$)

If the women who are ER- could be identified, then restricting the analysis to the other women would increase the apparent absolute survival benefit from 14 per 1000 to 25 per 1000. More importantly, it would also change the 2p-value from 0.1 (not significant) to 0.01, replacing a false negative with a clearly significant positive survival result. In ATLAS, we propose (after excluding the few we already know to have ER- disease) to seek the ER status in the many cases where it is currently missing. These additional ER assays would change about 20% of those who are currently in the "ER+ or ER untested" category into ER-, after which the arithmetic would be as in the foregoing table. (Note, however, that as the few patients in ATLAS we already know to have had ER- disease are excluded entirely, the "ER-" category would consist only of those newly discovered to have ER- disease.)

Almost all of the patients in ATLAS currently have ER+ or, more commonly, unknown ER status. About 20% could be newly shown to have had ER- disease by retrospective retrieval and measurement of stored biological samples, such as slides or pathology blocks. If, in this 20% of "newly ascertained ER-" women, the apparent treatment effect happens by chance to be somewhat unfavourable for 10 years of tamoxifen, then doing the tests that identify them would make the p-value for all-cause mortality among the other women much more extreme. Moreover, their exclusion would help reveal the true effect of 10 years versus just 5 years of adjuvant tamoxifen among those women most likely to benefit, that is, those with ER+ disease, who form the majority of women with breast cancer. Whatever the p-value would be among the 8000 ER+ or untested women (we will not be able to ascertain the ER status of every single woman for whom no ER status is currently available) who remain after these 2000 ER- women have been identified and removed, the p-value if they were not identified and removed would have been much less extreme: Table 3.

Table 3: Three possible outcomes of ATLAS (comparing 10 years with 5 years adjuvant tamoxifen), if 2000 ER- patients with a non-significant adverse effect of continued tamoxifen (280 vs 250 deaths, $2p > 0.1$, as in Table 2) are identified and removed.

	Results if 2000 women with ER- disease are NOT removed (5000 vs 5000)	Results among the 2000 women with ER- disease (1000 vs 1000)	Results in women with ER+ disease (or ER untested) if 2000 ARE removed (4000 vs 4000)
I.	1180 vs 1250 ($2p = 0.10$)	280 vs 250 ($2p > 0.1$)	900 vs 1000 ($2p = 0.01$)
II.	1155 vs 1250 ($2p = 0.03$)	280 vs 250 ($2p > 0.1$)	875 vs 1000 ($2p = 0.001$)
III.	1140 vs 1250 ($2p = 0.01$)	280 vs 250 ($2p > 0.1$)	860 vs 1000 ($2p = 0.0001$)

In conclusion, if there is, just by the play of chance, a non-significant adverse effect of continued tamoxifen in 2000 ER- women who could be identified retrospectively, then identification and removal of these women will increase the apparent size of the treatment effect among women with ER+ (or ER untested) disease and will also make the p-value very much more extreme (e.g. 0.01 instead of 0.1, or 0.0001 instead of 0.01).

It is the above scientific rationale that has led us to retrieve the original tumour blocks/specimens of women in ATLAS who are of unknown ER status and then to perform a retrospective ER assay.

C. BODY OF THE REPORT

Review of statement of work

The current report will focus on those achievements since the final report was submitted and approved. The initial funding from the US Army successfully established the infrastructure for this international collaboration, and supported the early stages of the trial's implementation. The first stage of ATLAS has now mainly been completed — that is, the development of a wide-scale collaborative group and the establishment of the materials and procedures needed for the smooth conduct of the trial. But these largely administrative activities have now been translated into actual accrual of patients and their follow-up within ATLAS. ATLAS has now (June 2000) recruited more than 6000 women and successfully completed four annual follow-ups on women in the study. In August 1999 onwards, the ATLAS Patient Identification and Registration Project was implemented (see below), and the ATLAS Oestrogen Receptor Detection Project was piloted. These projects have the potential to increase accrual to the study and to increase the scientific value and reliability of the study results, respectively. They are described in detail in the report.

Statement of Work since final report

1998 - onwards	Recruitment period (to continue to 2005)
1999 -	ATLAS Patient Identification and Registration Project ATLAS Oestrogen Receptor Detection Project
Late 2000-early 2001	Re-launch of ATLAS internationally following the next EBCTCG meeting in September 2000
Annual	Follow-up (to continue to 2010) Data Monitoring Committee meeting Steering Committee meeting
Quarterly	ATLAS Newsletter

Status of the ATLAS collaboration: June 2000

- 400+ centres with ethics approval
- 319 centres actively randomising in 30+ countries
- 7200 women registered with ATLAS
- 6200+ women randomised
- 4 cycles of annual follow-up completed
- Current accrual rate should continue to increase
- Significantly increased accrual anticipated in 2000

Maintaining and strengthening the ATLAS collaboration

Once the initial step of establishing the collaboration was completed, the next phase in the trial was and remains to maintain, strengthen and extend the collaboration within each country, and to ensure active participation in ATLAS. In view of the scale of the collaboration, this has been achieved mainly through close collaboration between Oxford and each of the national coordinators, who are then responsible for coordinating the clinical network in each of their respective countries. The international coordinating centre still undertakes the bulk of the administrative workload and has overall responsibility for coordination and management of the trial. However, Oxford is dependent on the support of the various national coordinators, each of whom is a member of the ATLAS Steering Committee.

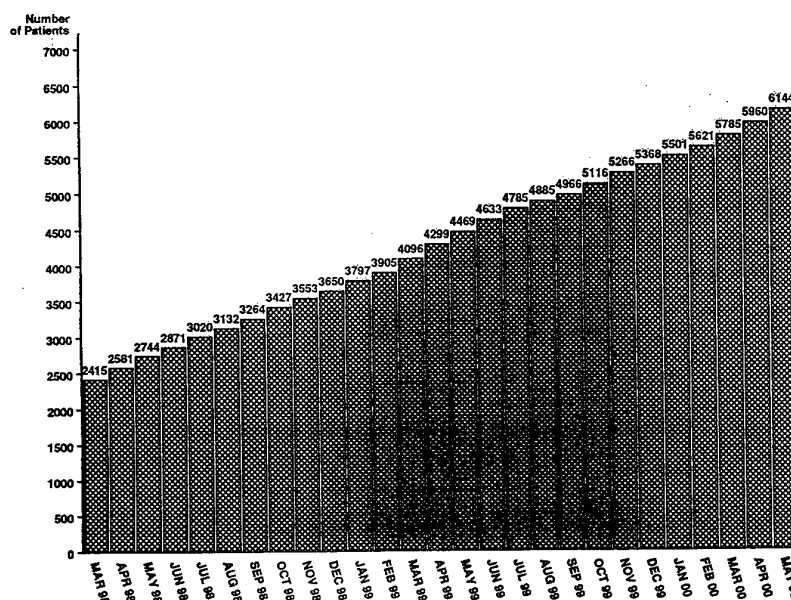
Current global accrual

	November 1996	November 1997	November 1998	June 2000
Centres with ethics approval	154	253	335	400+
Global accrual	469	1867	3500	6200+

No local ethics committee has declined to approve ATLAS and it is anticipated that several hundred hospitals should eventually participate.

Figure 4: Cumulative accrual to ATLAS world-wide

ATLAS Randomisation: Global Cumulative Accrual to 31/5/2000



Expanding the collaboration and increasing recruitment

In the final report to the US Army, we reported that there were still some countries still expected to make a major contribution to ATLAS in terms of patient accrual, notably, Spain, Argentina and Italy. Of these, Spain and Argentina have made significant progress: the situation in Italy remains uncertain due to problems associated with regulatory approval from the Ministry of Health. We are still hopeful that these problems can be resolved. However, ATLAS is now being extended to the United States, and to China, and these countries, China in particular, are expected to make important contributions to the trial. The trial will formally be launched in China towards the end of 2000.

Progression of ATLAS over the next few years and into the millennium

If current accrual rates continue, the accrual target of 10,000 - 20,000 women will be reached in mid-2005. However, we anticipate that three major factors will contribute to increased accrual around the year 2000.

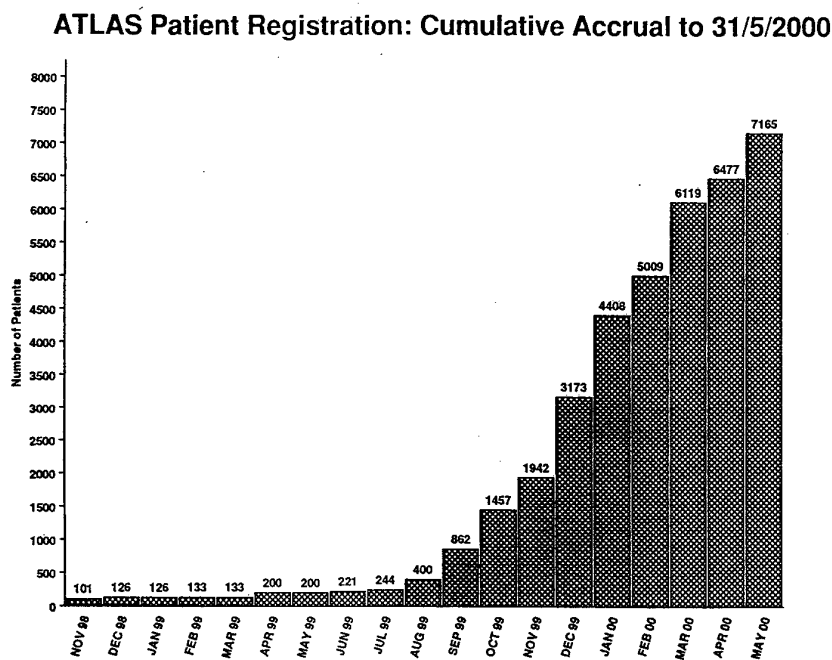
Firstly, the earlier lag in accrual as clinicians were shifting to using 5 years of tamoxifen routinely should largely have disappeared by the end of the year 2000 - the latest EBCTCG Overview was published in mid-1998² and we would anticipate that by the end of the year 2000/early 2001, many of the women who have been on tamoxifen now for 2 or 3 years will, by then, be ready to be randomised into ATLAS.

Secondly, the next cycle of the EBCTCG in September 2000 is likely to conclude that 5 years of adjuvant hormonal treatment is definitely better than just 2 years, and the question of whether 10

years is better than 5 years will then become even more pertinent. Since the meta-analysis is co-ordinated by this department, we are in contact with those trialists contributing to the EBCTCG who may have an interest in collaborating in ATLAS. Any increased collaboration could boost accrual further such that the accrual target could be reached as early as mid-2005.

Thirdly, and most importantly, the ATLAS Patient Identification and Registration Project has been implemented during 2000 and will continue during the coming years. One difficulty in the trial that has emerged as the trial has progressed is the identification of potentially eligible women, given that they are clinically free from disease and some years away from their original diagnosis. In order to identify quickly several tens of thousands of women currently on tamoxifen, a system of registration of women prior to completion of their first five years of tamoxifen and identification of women who might now be eligible for ATLAS has been organised. ATLAS helps to cover the costs of reviewing all of the patient records of all living breast cancer patients in a collaborating hospital, finding a large number of patients who are on tamoxifen, and registering each of them with the ATLAS Office. As these women approach being on tamoxifen for about 5 years, a reminder is then sent to the clinician to consider randomising the patient in the study. So far, more than 7000 women (in less than 1 year) have been registered with the ATLAS Office (figure 5) and it is anticipated that this will increase rapidly to several tens of thousands in the next 2-3 years, a significant proportion of whom will subsequently be randomised in the trial. This project has been facilitated in certain countries by the availability within ATLAS of free tamoxifen for registered women, to enable women to receive 5 years of tamoxifen prior to randomisation, as considered clinically appropriate.

Figure 5: Registration of patients in ATLAS



ATLAS Oestrogen Receptor Detection Project

The scientific rationale for this has been set out above. This project has been piloted and will be implemented world-wide during 2000-2001. The aim is to ensure that as many women who are either registered or randomised will have an ER status available. In each participating country, a central clinical reference laboratory is being identified, which is responsible, under the supervision of an ATLAS collaborator, for retrieving the original tumour blocks/specimens, transferring these to the laboratory and performing the assays. The results of the assays will be centrally recorded in Oxford.

Annual follow-up

In ATLAS, long-term follow-up of all randomised patients is fundamental and will continue for at least 10 years on each randomised patient. In view of the varying health care systems, and management patterns and the availability (or not, as the case may be) of national cancer registration/mortality statistics records in collaborating countries, it has been essential to ensure that appropriate mechanisms are in place for long-term follow-up of women randomised in the different countries. Follow-up takes place on 1 January each year when data is requested on all patients randomised up to the previous October so that data are available in time for the annual Data Monitoring Committee meeting. Two reminder letters are sent out in March and July for unreturned forms, and then the minority of forms not returned are collected throughout the remainder of the year. The fifth annual follow-up will place in January 2001.

Doctors are requested to provide the information as soon as possible - because of the simplicity of the data request and the mechanisms in place to ensure follow-up in all patients in all countries, it is anticipated that there will be minimal loss to follow-up. The Data Monitoring Committee for ATLAS reviews the follow-up data annually along with other aspects of the conduct of the trial, and information relevant to the study.

4th meeting of the ATLAS independent Data Monitoring Committee

The Data Monitoring Committee meets on an annual basis and its terms of reference are set out in the trial protocol. The Committee held a telephone conference call in June 1999 and reviewed the progress of ATLAS and data from other adjuvant tamoxifen duration studies. The independent ATLAS Data Monitoring Committee confirmed the continued need for ATLAS and concluded in particular that the stoppage of one of the trials of 5 years of tamoxifen versus 10 years (NSABP B-14) may well, in time, be shown to have been premature. The Committee was satisfied with all aspects of the progress of the trial, noting the steady increase in ethics approval and patient accrual. The Committee unanimously approved the continuation of the trial with the present protocol and patient information sheet. The Chairman of the Committee informed Dr Chris Williams (Chairman of the ATLAS Steering Committee) of these conclusions. The Committee will have its next meeting in September 2000 to review progress and the Chairman will take any interim decisions as appropriate.

ATLAS relaunch

Following the next cycle of the EBCTCG in September, ATLAS national collaborators' meetings will be held world-wide. The aim of these meetings will be to present the EBCTCG results, to reaffirm the importance of ATLAS, and to encourage active participation in the trial, in particular in the ATLAS Patient Identification and Registration Project, and in the ATLAS Oestrogen Receptor Detection Project.

D. CONCLUSIONS

Since the time of the final report, ATLAS has continued to progress towards its main objective of randomising 10,000-20,000 women between 5 and 10 years of adjuvant tamoxifen. The accrual target for ATLAS should be reached by 2005. This should be facilitated by the new system of patient registration.

The US Army has now provided 5 years of funding but continued funds are requested from the US Army Breast Cancer Program. ATLAS has obtained funding for the ATLAS Oestrogen Receptor Detection Project, but to help with the ATLAS Patient Identification and Registration Project, to complete accrual and to ensure long-term follow-up of women randomised additional funding is needed. If the US Army does provide additional support, this should not only help to ensure that the main objective of the trial is fulfilled but also that the scientific returns on the initial investment are realised (Section E justifies this request for funding in further detail).

E. REQUEST FOR ADDITIONAL FUNDING FROM THE US ARMY BREAST CANCER RESEARCH PROGRAM

The initial stages of ATLAS have been successfully completed with existing support. The funding from the European Community Biomed Program (400k ECU over 3 years) to cover some of the coordinating costs of ATLAS in 5 European countries (namely, Spain, Italy, Israel, Poland and the Czech Republic) will end in 2001. In addition the UK Imperial Cancer Research Fund - the main funding body of the Department has provided funding to cover the central personnel costs of ATLAS and to absorb some of the running costs of the trial. However, further funding is required to support the collaboration worldwide, in particular to support the ATLAS Patient Identification and Registration Project and to ensure long-term follow-up of women randomised. The former is of particular importance if the accrual target is to be met as quickly as possible, but long-term follow-up is also critical. Only those costs that cannot be met from other sources are being requested from the US Army.

Justification for continued support

Now that the collaboration is in place, the international coordinating centre is reliant on the continued enthusiasm and active participation of ATLAS collaborators. Even though ATLAS is streamlined with simple procedures for the entry and follow-up of eligible women, it still takes time and effort to identify patients, obtain informed consent, randomise, and provide long-term follow-up information. Hence, the balance of resource needs has changed with time, so that more resources are now required at the national and local levels, and relatively less support is required centrally.

National and local resource requirements:

National coordinator: Support is required for the coordination of the study within each country by the national coordinators who help to maintain an active collaboration in their country and resolve any local problems that may arise. In some countries, the network of clinicians is only small, and Oxford can help to meet the costs that might be incurred. However, in countries with large clinical networks, for example in countries like Chile, Argentina, Australia, India, Italy, and Spain, there are more than 30 centres actively participating in the study and maintaining contact with these centres involves time and resources. The international coordinating centre has been successful in obtaining funding from the European Community for the coordination of ATLAS in centres in Europe, but support is needed to cover the national coordinating centre running costs in other countries. The main costs that need to be met concern communication with local centres, travel costs to enable the national coordinator to visit new and existing centres to encourage participation, mail-shots to collaborators nationwide to inform them of progression ATLAS in the local language (which could not be done easily and as cheaply from Oxford), and secretarial costs.

ATLAS Patient Identification and Registration Project: Identifying potentially eligible women is crucial to the success of the study. Since these are women who were diagnosed with breast cancer some time ago and who are clinically free from disease, systematic identification of those on tamoxifen who may be eligible either now or at some point in the future can involve sorting through many records. Support for a nurse/data manager for 1-2 days each month in each centre that is likely to recruit large numbers would allow this record search to take place. More than 7000 women have already been registered, but ATLAS needs to register at least 30,000. A large proportion of these women can then subsequently be considered for randomisation in ATLAS.

Central resource requirements: These will be met through other sources.

ATLAS Oestrogen Receptor Detection Project: This will be supported from other sources.

Follow-up costs: We estimate that this will be at least £10 per patient for the duration of the trial.

Communication costs: Postage cost estimates are based on the expectation of between 4-5 letters per collaborator per year. Freephone lines have been established to enable collaborators to

use the telephone randomisation facility without costs, making it easier to enter patients into the trial and to seek further information.

Travel costs: In view of the international scope of the trial and its multicentric status, it is fundamental that there should be sufficient travel resources available to allow the clinical coordinator to visit many of the participating centres, to maintain enthusiasm for the trial, to monitor participation and to resolve any serious problems which might develop. It will be necessary to ensure that complete data are obtained on all patients randomised and, in some cases, this may require extraction of the data directly from participating hospitals.

Supply of free tamoxifen: The ATLAS Office was successful in obtaining free Nolvadex from Zeneca Pharmaceuticals plc for all of those women randomised to continue treatment and in some countries, for registered women. Funding is required for its distribution to collaborating centres.

Table: Estimate of future funding requirements

Support required for:	Level of support required per annum
National and local coordination costs: Support for national coordinators to encourage active participation of clinicians in that country in particular in India, Chile, Argentina, Australia, Brazil and China (other countries with large clinical networks covered by EC support)	£50k
Patient Identification and Registration Project: Local costs to cover the identification of potentially eligible patients for ATLAS (based on £10 per patient registered and a registration target of 30,000)	£100k
Follow-up: Based on £10 per patient and an eventual trial size of 20,000	£200k (in total)
Central running costs: Travel Meeting costs Drug packing and distribution world-wide Communication (telephone/fax/mail)	£35k £15k £30k £10k
Total annual cost:	£240k per annum plus £200k for follow-up
Three year costs:	£720k plus £200k for follow-up

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